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Impact of vascular diseases on the progression of mild cognitive impairment to Alzheimer's disease

Wpływ obciążenia chorobami naczyniowymi na progresję łagodnych zaburzeń poznawczych do choroby Alzheimera

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Abstract

Introduction: Mild cognitive impairment does not meet the criteria for the diagnosis of dementia, but reaching this diagnosis raises concern about the future state of a patient due to the possibility of the conversion to Alzheimer's disease. Although the aetiology of Alzheimer's disease is neurodegenerative, the impact of vascular diseases is also taken into consideration. **The aim of this study** was to assess the impact of vascular diseases in patients diagnosed with mild cognitive impairment on the conversion to Alzheimer's disease. **Material and methods:** In each of 101 patients with a diagnosis of mild cognitive impairment, a detailed medical history was taken, taking into account: hypertension, ischaemic heart disease, arrhythmias, myocardial infarction, stroke, diabetes as well as thyroid diseases, head injuries, alcohol abuse, smoking, exposure to toxic substances, surgery under general anaesthesia and the family character of dementia. Clinical follow-ups were scheduled after 6, 12 and 24 months. **Results:** Amongst 101 patients with mild cognitive impairment, 17 (16.8%) converted to Alzheimer's disease within two years of observation. The analysis of the distribution of independence tests showed that the conversion is significant for two variables: ischaemic heart disease and myocardial infarction.

Key words: mild cognitive impairment, conversion, Alzheimer's disease, myocardial infarction, ischaemic heart disease

Streszczenie

Wstęp: Łagodne zaburzenia poznawcze nie spełniają kryteriów rozpoznania zespołu otępiennego, jednakże ustalenie tego rozpoznania wzbudza obawę o przyszły stan pacjenta, w związku z zagrożeniem konwersją do choroby Alzheimera. Mimo etiologii zwyrodnieniowej choroby Alzheimera brany pod uwagę jest również wpływ chorób naczyniowych na rozwój tej choroby. **Celem pracy** była ocena wpływu obciążenia chorobami naczyniowymi u pacjentów ze zdiagnozowanymi łagodnymi zaburzeniami poznawczymi na konwersję do choroby Alzheimera. **Materiał i metody:** U 101 pacjentów z rozpoznaniem łagodnych zaburzeń poznawczych przeprowadzono szczegółowy wywiad chorobowy, uwzględniający: nadciśnienie tętnicze, chorobę niedokrwienną serca, zaburzenia rytmu serca, zawał serca, udar mózgu, cukrzycę, a ponadto choroby tarczycy, urazy głowy, nadużywanie alkoholu, nikotynizm, kontakt z substancjami toksycznymi, operacje w znieczuleniu ogólnym i rodzinność otępienia. Zaplanowano wizyty kliniczne po 6, 12, 24 miesiącach. **Wyniki:** Spośród 101 pacjentów z rozpoznaniem łagodnych zaburzeń poznawczych u 17 osób (16,8%) stwierdzono konwersję do choroby Alzheimera w ciągu 2 lat obserwacji. Analiza testów niezależności rozkładów wykazała, że konwersja jest istotna dla dwóch zmiennych: choroby niedokrwiennej serca oraz zawału serca w wywiadzie.

Słowa kluczowe: łagodne zaburzenia poznawcze, konwersja, choroba Alzheimera, zawał serca, choroba niedokrwienna serca

INTRODUCTION

Mild cognitive impairment (MCI) is a cognitive dysfunction, but does not meet the criteria for the diagnosis of dementia. Patients with MCI can present stable, non-progressive symptoms until the end of their lives, but the progression of the disease (usually gradual), leading to the development of dementia, can also be observed. It is estimated that the percentage of the conversion to Alzheimer's disease (AD) is about 10–15% per year (Petersen *et al.*, 2009). In the diagnostic criteria for AD (McKhann *et al.*, 2011), MCI is a stage of Alzheimer's neuropathological process (between the predictive phase and the phase of AD dementia). The time to progression of MCI to AD is very important from a clinical point of view because therapeutic effects are the most effective in early stages of AD. However, there is no established, recommended treatment of MCI.

The aim of the study was to assess the impact of vascular diseases in patients diagnosed with MCI on the conversion to AD. According to Lathe, AD and atherosclerosis may have partly common pathoaetiology due to inflammatory factors, influence of ApoE protein and other genetic factors (Lathe *et al.*, 2014). Lathe also notes the impact of β-amyloid and its precursors on lipid metabolism, and thereby on the formation of atherosclerotic plaques.

MATERIAL AND METHODS

One hundred and one patients aged 50–80 (mean age 62.7) diagnosed with MCI (according to the diagnostic criteria from 2004; Winblad *et al.*) were enrolled in the study. In each patient, a detailed medical history was taken, taking into account: hypertension, ischaemic heart disease, arrhythmias, myocardial infarction, stroke, diabetes as well as thyroid diseases, head injuries, alcohol abuse, smoking, exposure to toxic substances, surgery under general anaesthesia and the family character of dementia.

Neurological assessment, MMSE (Mini-Mental State Examination), CDT (clock drawing test) and GDS (Global Deterioration Scale) were performed. The average score of MMSE was 27.4/30 (range 25–30 points). Laboratory tests included CBC, TSH, blood glucose, urea, creatinine, transaminases, VDRL test (venereal disease research laboratory) as well as levels of vitamin B_{12} and folic acid. There were no significant abnormalities. Each patient was assessed using standard neuropsychological tests. On CDR scale (Clinical Dementia Rating), all patients received the score of 0.5 or 0/0.5. For each patient, follow-up visits were scheduled after 6 months (±14 days), 12 months (±30 days) and 24 months (±50 days). Subsequently, patients were re-assessed using MMSE, CDT and GDS scales and re-examined neurologically and neuropsychologically to assess potential disease progression. In patients diagnosed with the conversion to AD, acetylcholinesterase inhibitor treatment was initiated. All patients remain under the care of the Memory Disorders Outpatient Clinic of the Hospital of the Ministry of Interior in Warsaw.

Brain MRI was performed in each of the patients to exclude other causes of cognitive impairment (tumours, extensive vascular changes, normotensive hydrocephalus, etc.).

RESULTS

Seventeen of 101 patients (16.8%) diagnosed with MCI converted to AD within two years of observation. In the first follow-up visit after 6 months (±14 days), conversion was observed in 9 patients, that is in 52.9% of all patients with the progression of MCI to AD during the observation period and 8.9% of the whole study population. In the next visit after a year (±30 days), the conversion to AD was diagnosed in the next 7 people (6.9% of all patients), and during the whole year, progression was observed in 16 patients (15.8%). Throughout the next year of observation (2 years after the first visit ±50 days), conversion occurred in one person – 0.99%.

The analysis of the distribution of independence tests showed that the conversion is significant for two variables: ischaemic heart disease (IHD) (chi-square = 8.654, $p = 0.003$, p_Fisher's = 0.008) and a history of myocardial infarction (chi-square = 11.317, $p = 0.001$, p_Fisher's = 0.007). Detailed test results for all variables are presented in Tab. 1.

In the group of patients with IHD, the progression to AD was observed in 41.2% of patients whereas among patients without IHD, 88.1% did not convert to AD. A similar relationship was found in the case of myocardial infarction: 66.7% patients with a history of myocardial infarction (MI) converted to AD while 86.3% of patients without a history of MI did not progress to AD.

As for other variables, only age was positively verified due to the nature of the normal distribution, and only in this case can the data in Tab. 2 be analysed. This variable differentiates the two groups of patients to the greatest degree ($t = -5.045$, $p < 0.001$).

Tab. 3 shows that the average age difference between patients who converted to AD and patients with stable MCI was 11.1 years.

DISCUSSION

There are many reports in the literature concerning the impact of cerebrovascular diseases on the development of dementia. These vascular episodes are usually not severe strokes that may precede symptoms of AD (Mayeux and Stern, 2012; Pendlebury and Rothwell, 2009; Schneider and Bennett, 2010). In our study, stroke was not found statistically significant, probably due to the fact that patients with extensive vascular lesions in the brain were excluded from the study.

In our study, the conversion was significant for two variables: ischaemic heart disease and myocardial infarction (both

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	Chi-square		Fisher's exact test (significance)
	Value statistics	Significance	
Family history of dementia	1.962	0.161	0.185
Hypertension	2.689	0.101	0.117
Ischaemic heart disease	8.654	**0.003****	0.008
Arrhythmias	3.334	0.068	0.119
Myocardial infarction	11.317	**0.001****	0.007
Stroke	0.000	0.991	1.000
Diabetes	1.922	0.166	0.174
Thyroid diseases	1.085	0.581	0.581
Head injuries	0.205	0.651	0.759
Alcohol abuse	0.000	0.991	1.000
Smoking	1.036	0.309	0.385
Exposure to toxic substances	1.291	0.256	0.586

Tab. 1. Results of significance and chi-square tests, Fisher's exact test of independence

	KS normality test	Levene's homogeneity of variance		Mean difference for independent samples in a student's *t*-test			
	Significance	*F*	Significance	*t*	Degrees of freedom	Significance (two-sided)	Average difference
Age	0.054	1.254	0.266	–5.045	99	0.000	–11.120
Education	0.000	0.235	0.629	0.871	85	0.386	0.6778
MMSE	0.012	0.055	0.814	2.176	98	0.032	0.966
GDS	0.000	2.659	0.106	–5.745	97	0.000	–0.866
Doses of anaesthetic	0.000	4.047	0.047	0.933	97	0.353	0.268

Tab. 2. Results of a t*-test concerning the difference of mean values for independent samples*

	Non-converters (*n* = 84)		Converters (*n* = 17)		Total (*n* = 101)	
	Average	Standard deviation	Average	Standard deviation	Average	Standard deviation
Age	**60.8**	8.2	**71.9**	8.7	**62.7**	9.2
MMSE	**27.6**	1.7	**26.6**	1.4	**27.4**	1.7
GDS	**2.6**	0.6	**3.5**	0.5	**2.8**	0.7

Tab. 3. Descriptive statistics in the subgroups of patients

diseases affect the coronary arteries). Other vascular factors such as arrhythmias, hypertension or diabetes proved to be statistically insignificant in our study although they are considered to be risk factors for Alzheimer's dementia (especially late-onset AD) (Mayeux and Stern, 2012; Peila *et al.*, 2002; Wu *et al.*, 2003). Interesting results were presented by Italian authors who studied the impact of cardiovascular risk factors (hypertension, hyperlipidaemia, diabetes mellitus type 2, smoking, carotid atheromasia) on the progression of MCI to AD. The percentage of conversion was almost twice higher in the group with cardiovascular risk factors (60% *vs.* 32%) (Ettore *et al.*, 2012). Similar results were obtained by Li in a study conducted among over 600 patients. He claimed that vascular risk factors (VRF) increased the risk of MCI to AD conversion. The following VRF proved to be statistically significant: hypertension, diabetes, hypercholesterolaemia and cerebrovascular disease. Moreover, it was found that the treatment of hypertension, hypercholesterolaemia and diabetes reduced AD conversion compared to patients with untreated VRF (Li *et al.*, 2011). It is also suspected that even in the course of AD, effective treatment of vascular diseases can slow the progression of dementia (Deschaintre *et al.*, 2009). Our study population was smaller than in Li's study, and our observation period was also shorter (2 years *vs.* 5 years). Furthermore, the percentage of diabetic patients in our study was low (less than 8%) and cholesterol level was not determined. Surprising results were also presented by Ravaglia. His patients who converted to AD had significantly lower blood pressure, lower cholesterol level and lower BMI. Additionally, atrial fibrillation and low level of folic acid occurred to be predictors of conversion (Ravaglia *et al.*, 2006).

In our study, the hypothesis that age is a risk factor for AD was also confirmed. Converters were on average 11.1 years older than non-converters.

There was no statistical significance for a correlation with education (years of education), a positive family history of AD, smoking, alcohol abuse, thyroid diseases, head injuries or the use of general anaesthesia in the past.

The probability of progression to AD seems to be higher in patients with MCI and coronary artery disease.

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Conflict of interest

The authors do not report any financial or personal links with other persons or organizations, which might affect negatively the content of this publication or claim authorship rights to this publication.

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